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| 10/520,457 | 11/30/2005 | Caroline Connolly | FDEHN7.001APC | 5613 |

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| EXAMINER | |
|---|---|
| SCHUBERG, LAURA J | |

| ART UNIT | PAPER NUMBER |
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| 1657 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/520,457 | CONNOLLY ET AL. | |
| | Examiner | Art Unit | |
| | LAURA SCHUBERG | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9 and 11-15* is/are pending in the application.

4a) Of the above claim(s) *9 and 11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 14 and 15* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/25/06 6/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election of Group I (claims 1-8, 14 and 15) in the reply filed on 04/28/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-9, 11-15 are pending.

Claims 9 and 11-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-8, 14 and 15 have been examined on the merits.

### *Claim Objections*

Claim 8 is objected to because of the following informalities: As currently written, claim 8 is drawn to the method of 1 or 3. It appears that Applicant intends the method of claims 1 or 3 and the term "claims" should be inserted prior to 1 or 3.

Claim 8 is also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The test for a proper dependent claim is whether the dependent claim includes every limitation of the parent claim. A proper dependent claim shall not conceivably be infringed by anything

which would not also infringe the basic claim. Since dependent claim 8 requires different method steps from parent claim 1, claim 8 does not further limit claim 1 and is an improper dependent claim.

Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kraus et al (US 5,143,838) in view of Anderle et al (US 2003/0133829).

Claim 1 is drawn to a method for the preparation of virus-inactivated thrombin comprising a) solvent-detergent virus inactivating of a solution comprising prothrombin and factor X; b) loading the product of step a) onto an anion exchange medium; c) washing the anion exchange medium to remove reagents used for step a); and d) activating the prothrombin on the anion exchange medium to form thrombin by addition of metal ions.

Dependent claims include wherein the solution is prothrombin complex (claim 2), the type of metal ions (claims 4 and 5), further comprising the steps of e) selectively eluting the thrombin from the anion exchange medium (claim 6), replacing steps a) and b) with steps a') and b') wherein a') is loading a solution comprising prothrombin and factor X onto an anion exchange medium and b') is solvent-detergent virus inactivating of the prothrombin and factor X on the anion exchange medium (claim 8).

Claim 3 is drawn to a method for the preparation of virus-inactivated thrombin comprising a) solvent-detergent virus inactivating of a solution comprising factor X; b) loading the product of step a) onto an anion exchange medium; c) washing the anion exchange medium to remove reagents used for step a); and d) activating the factor X on the anion exchange medium to form factor Xa by addition of metal ions; and e) loading

virus-inactivated prothrombin onto the anion exchange medium such that thrombin is generated.

Dependent claims include the type of metal ions (claims 4 and 5), replacing steps a) and b) with steps a') and b') wherein a') is loading a solution comprising prothrombin and factor X onto an anion exchange medium and b') is solvent-detergent virus inactivating of the prothrombin and factor X on the anion exchange medium (claim 8), further comprising the step of f) selectively eluting the thrombin from the anion exchange medium (claim 14).

Kraus et al teach a method of producing thrombin from prothrombin using calcium ions for the conversion on an anion exchange medium. The includes a solution, preferably human blood plasma or a fraction thereof, that contains Factor II (prothrombin) is adsorbed onto an anion exchange medium (column 2 lines 26-36). For elution a buffer that contains an activator –calcium ions, calcium ions plus thromboplastin or Factor Xa are applied to the matrix. The plasma or plasma fraction is activated into thrombin with the buffer solution by eluting the matrix (column 2 lines 37-49). Filtration of the thrombin is suggested and taught to increase purity (column 2 lines 58-61). Before or after the thrombin is isolated from the plasma or plasma fraction the batch can be sterilized to inactivate human-pathogenic viruses by treatment with detergent or by heating (column 3 lines 1-7).

Kraus et al do not teach solvent-detergent inactivation on the anion exchange medium or freeze-drying the thrombin product.

Anderle et al teach a process for inactivating pathogens in a biological material. The solvent-detergent virus inactivating of a protein solution, the subsequent adsorption to an anion exchange medium (DEAE sephadex), washing of the protein loaded anion exchange medium, elution of the proteins and filtration are taught (pages 7-8, examples 4 and 7). In addition to protein enrichment steps, the protein may also be purified either before or after the treatment disclosed (page 5 para 58). Exemplary proteins include coagulation factors such as FII (prothrombin) and FX and FEIBA (activated prothrombin complex concentrate) (page 5 para 57 and page 6 para 66). The method is taught to be a gentle, effective procedure for inactivating pathogens in a protein solution, which does not substantially reduce the activity of a selected protein in the solution (page 2 para 12).

Therefore, one of ordinary skill in the art would have been motivated to apply the solvent-detergent inactivating steps of Anderle et al to the method of Kraus et al because Anderle et al teach that these steps are a gentle, effective procedure for inactivating pathogens in a protein solution, which does not substantially reduce the activity of a selected protein in the solution (page 2 para 12) and Kraus et al had also suggested using detergent it inactivate viruses (column 3 lines 1-7). One of ordinary skill in the art would have had a reasonable expectation of success of combining these methods because both Kraus et al and Anderle et al were teaching the purification of proteins such as plasma fractions.

M.P.E.P. § 2144 recites, "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or

impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law…If the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." In *In re Burhans, 154 F.2d 690, 69 USPQ 330* (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. In *In re Gibson, 39 F.2d 975, 5 USPQ 230* (CCPA 1930), the court found that selection of any order of mixing ingredients is *prima facie* obvious.

Therefore the combined teachings of Kraus et al and Anderle et al render obvious Applicant's invention as claimed.

Claims 7 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kraus et al (US 5,143,838) in view of Anderle et al (US 2003/0133829) as applied to claims 1-6, 8 and 14 above, and further in view of Kingdom et al (US 5,354,682) and Heimburger et al (US 6,346,277).

Claim 7 is drawn to the method of claim 6 further comprising the steps of f) passing the product of step e) through a filter which retains pathogens, step g) adding a divalent metal ion and a carbohydrate to the product of step f), step h) freeze-drying and heat-treating the product of step g) to inactivate viruses.

Claim 15 is drawn to the method of claim 14, further comprising the steps of g) passing the product of step f) through a filter which retains pathogens, h) adding a divalent metal ion and a carbohydrate to the product of step g), step i) freeze-drying and heat-treating the product of step h) to inactivate viruses.

The combined teachings of Kraus et al and Anderle et al render obvious Applicant's invention as claimed as described above. Heat treatment is suggested by Kraus et al as a suitable method for sterilization of the thrombin product (column 3 lines 1-7).

Kingdom et al teach that after elution from a capture means thrombin may be further processed through lyophilization, ultrafiltration and other conventional methods. Stability of the final thrombin product is enhanced by infusion of starch, dextran, or combinations thereof (carbohydrates) and packaged for drug use (column 5 line 64-column 6 line 7).

Heimburger et al teach that to destroy the hepatitis viruses in a blood plasma fraction it is beneficial to add calcium ions and sucrose to a blood plasma fraction prior to heat treatment to increase the stability of the final product (column 5 lines 25-30). The product subject to this treatment can also be supplied in freeze-dried form as well (column 6 lines 34-40).

Therefore one of ordinary skill in the art would have been motivated to freeze–dry the thrombin product because Kingdom et al teach that it is suitable to do so and would have allowed the thrombin to be stored for long periods of time. One of ordinary skill in the art would have been motivated to add agents (such as carbohydrates) to enhance

the stability of the thrombin product because Kingdom et al suggests that it is beneficial to do so. One of ordinary skill in the art would have been motivated to add calcium ions with a carbohydrate such as sucrose because Heimburger et al teach that these agents will increase the stability of a blood plasma fraction upon heat treatment for the killing of hepatitis viruses and because Kraus et al suggests that it is beneficial to heat treat thrombin. One of ordinary skill in the art would have had a reasonable expectation of success because the references are all drawn to increasing the sterility and stability of blood plasma fractions and because Kingdom et al teach that conventional methods may be used to further process the thrombin product.

Therefore the combined teachings of Kraus et al, Anderle et al, Kingdom et al and Heimburger et al render obvious Applicant's invention as claimed.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14 and 21 of copending Application No. 10/520,436. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application include all the method steps of the current claims and thus anticipate these claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg